Calanolide A

Drug Class: **Non-nucleoside Reverse Transcriptase Inhibitors**

Drug Description

Calanolide A, a novel dipyranocoumarin from the Malaysian tree Caulophyllum lanigerum var. austrocoriaceum, is a representative of a distinct class of HIV-1 specific nonnucleoside reverse transcriptase inhibitors (NNRTIs). Synthetic (+/-)-calanolide A has been chromatographically resolved into its optically active forms. Only the (+)-calanolide A has anti-HIV activity. [1]

HIV/AIDS-Related Uses

Calanolide A is a novel NNRTI with potent in vitro activity against HIV-1 and unique pharmacokinetic properties. In vitro studies have demonstrated the protective activity of calanolide A against a wide variety of HIV-1 isolates, including synctium-inducing and non-synctium-inducing strains and both T cell tropic and monocyte-macrophage tropic strains.[2] Calanolide A is currently in Phase Ib studies for the treatment of HIV in combination therapy.[3]

Non-HIV/AIDS-Related Uses

Calanolide A may be active against Mycobacterium tuberculosis and human cytomegalovirus.[4]

Pharmacology

Calanolide A inhibits HIV-1 but is essentially inactive against HIV-2. Viral life cycle studies indicated that calanolide A acts early in the infection process, similar to the nucleoside reverse transcriptase inhibitor (NRTI) zalcitabine. In enzyme inhibition assays, calanolide A potently and selectively inhibits recombinant HIV-1 reverse transcriptase (RT) but not cellular DNA polymerases or HIV-2 RT.[5] Evidence suggests that one of the calanolide A binding sites is near both the pyrophosphate binding site and the active site of the RT enzyme.[6]

The safety and pharmacokinetics of a single dose of calanolide A were evaluated in 47 HIV uninfected adult volunteers. Pharmacokinetic parameters were highly variable. The half-life was 20 hours in those receiving an 800 mg dose, indicating that calanolide A may be suitable for once-daily dosing. Both the mean maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) values increased with increasing dose. Women appeared to have higher plasma drug levels and a longer elimination half-life than men; however, these differences may be due to differences in body weight. The 50% effective concentration (EC50) ranged from 0.02 to 0.5 microM.[7] [8]

The use of calanolide A as part of combination therapy was evaluated in a Phase Ib trial in 32 HIV infected patients. Twice-daily regimens for 14 days showed viral load reductions as dosages increased. No evidence of viral mutations was observed during the study period.[9]

In vitro synergy has been demonstrated between calanolide A and NRTIs, NNRTIs, and protease inhibitors. Calanolide A remains fully active against viral isolates with zidovudine and lamivudine resistance mutations.[10] [11] Calanolide A inhibited HIV-1 RT in a synergistic fashion with nevirapine, further distinguishing it from other NNRTIs. In vitro studies demonstrated that calanolide A has synergistic anti-HIV activity when used in combination with zidovudine, nevirapine, didanosine, and carbovir.[12]

Calanolide A has enhanced activity against viral isolates with the Y181C mutation, which confers resistance to other NNRTIs. Although calanolide A exhibits reduced activity against HIV-1 isolates with the K103N mutation, it remains fully active against viral isolates that express both the K103N and Y181C mutations.[13]

Adverse Events/Toxicity

A phase Ia single-dose, escalating-dose study in HIV-1 uninfected participants showed that calanolide A was generally well tolerated in doses up to 800 mg. The most common adverse events observed were an oily aftertaste and mild to moderate dizziness. Headache, eructation, and nausea were also reported; all of these were either mild or moderate. The only significant abnormal laboratory finding was a single report of Grade 3

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Adverse Events/Toxicity (cont.)

lipase elevation that was completely asymptomatic and resolved spontaneously.[14]

Drug and Food Interactions

Phase I trials indicate a high degree of variability in the effect of food on the pharmacokinetic profile of calanolide A. Further studies are needed.[15]

Clinical Trials

For information on clinical trials that involve Calanolide A, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Calanolide A AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[16]

Dosage Form: Soft gelatin capsules.[17]

Chemistry

CAS Name: 2H,6H,10H-Benzo(1,2-b:3,4-b':5,6-b') tripyran-2-one, 11,12-dihydro-12-hydroxy-6,6,10,11-tetramethyl-4-propyl-,(10R-(10alpha,11beta,12alpha))-[18]

CAS Number: 142632-32-4[19]

Molecular formula: C22-H26-O5[20]

C71.35%, H7.03%, O21.62%[21]

Molecular weight: 370.44[22]

Physical Description: Yellow-brown amorphous solid.[23]

Solubility: Slightly soluble in water. Soluble in methanol, ethanol, and a variety of other organic solvents. Also soluble in vegetable oils and propylene glycol.[24]

Other Names

(+)-Calanolide A[25]

Further Reading

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Manufacturer Information

Calanolide A
Sarawak MediChem Pharmaceuticals Inc
1440 Davey Road
Woodridge, IL 60517
(630) 739-6744

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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